MEIRU
Malawi Epidemiology and Intervention Research Unit
PO Box 46, Chilumba, Karonga District, Malawi.
Tel: + 265 1364 200/211/246, +265 999 971 860/1
Fax:+2651 364 256 E-mail: kpschilumba@lshtm.ac.uk
THE UNIVERSITY of EDINBURGH
UNC PROJECT Lilongwe, Malawi

PAPAGENO

STUDY: A pragmatic approach to preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource poor settings **(PAPAGENO).**

INTRODUCTION: You are being invited to join the PAPAGENO study because you are pregnant and have been identified by your doctor or midwife as being overweight. This leaflet contains information to help you decide if you would like to take part in the study. Ask the study team, if there is anything that is not clear or if you would like more information.

PURPOSE: The purpose of the PAPAGENO study is to help medical staff learn more about a tablet called Metformin which helps to improve both the mother's and baby's health in pregnant women with diabetes. We also know that women who are overweight are more likely to develop diabetes in pregnancy. Diabetes is when your body can't process the sugar from the food that you eat. When you are overweight in pregnancy not being able to process the extra sugar in your blood may increase pregnancy problems.

This is a feasibility l study to see if women are willing to be recruited to the PAPAGENO study. We will also gather information to help us design a larger study in the future. In addition, we also want to understand if taking the tablets sooner in pregnancy can prevent women from developing diabetes. . . Although there is no license to use metformin for diabetes treatment in pregnancy, it is widely used in the UK and New Zealand for this purpose. Some doctors believe taking metformin may also help prevent pre-eclampsia (high blood pressure) which some women develop when they are pregnant.

We hope that 100 pregnant women will agree to participate in the PAPAGENO study. We will give all of the women a tablet but half of the women (50) will be given metformin and the other half (50) will be treated with a placebo (dummy) tablet. The placebo will look the same as the metformin so neither you, nor the study doctors and midwives, will know who has been given metformin and who has been given the placebo tablets. This is called a double-blind study.

Your study team will not know which group you will be in as we try to make sure each patient is put into a group by chance (randomly). We are doing this because we want to see if we can prevent diabetes but we also need to learn more about which is the best way of treating overweight pregnant women.

WHY HAVE I BEEN ASKED TO TAKE PART? You have been asked to take part as you are overweight and pregnant and your study team think you are suitable to participate.

DO I HAVE TO TAKE PART? No, it is up to you to decide whether or not to take part. If you decide to take part you are still free to stop at any time and without giving a reason. Deciding not to take part or stopping the study will not affect the care that you receive. You may also wish to discuss the study with other family members before making a decision.

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WHAT WILL HAPPEN TO ME, IF I DECIDE TO TAKE PART?

Information Visit: Firstly, if your study team thinks you might be suitable you will be asked if you would like to take part in PAPAGENO you will read this leaflet or it will be read to you and you will be given time to consider. You can ask questions if you need to. If you agree, you will be asked to sign a consent form.

Consent: Once you agree and sign the consent form, this will be your first study visit (week 1 in your diary). You will be given a copy of the consent form and this information sheet to keep. Your doctor will keep the original consent form in the research study file and add a copy to your hospital notes. We will ask you some questions about you, your previous pregnancies and health.

Randomisation: You will be randomly allocated to one of the two groups to receive either metformin or placebo and given the tablets to take home with you. You will also be given a treatment diary to keep a record of the number of tablets you take each day; the diary should be taken to every monthly visit. Most women will take the first tablet in the evening, although your study team will advise you.

You will start by taking one tablet every evening with food. The tablets will increase slowly over a few weeks until you are taking four tablets each day. Your midwife or doctor will tell you how many tablets to take each day and your diary contains a reminder. You will stop taking the tablets, when your baby is delivered. **At that stage we will also collect information about how well you and your baby are.**

Monthly visits: You will be advised about your next visit but you should follow the usual schedule of attending the clinic until your baby is born which may be monthly or more often. During these visits we will ask you how you have been and to check you are taking your tablets. In one of the special study visits we will need to do a glucose tolerance test and we may also invite you to come to the clinic for the study data collection on other occasions. On each of these special study visits you will be given a sum of money (equivalent to $10) to help you with the cost of travelling to the hospital, food and compensation for your time.

A member of the study may also visit your household to confirm your location and collect a Global Positioning System (GPS) Reference this is to help us locate your household, if we need to contact you with information in the future.

At the hospital visit which occurs between your 24th and 30th week of pregnancy: You will have a glucose tolerance test. This is a blood test where a small amount of blood (about 5ml, a teaspoon) will be taken, using a needle. We will do this two times. The blood samples can only be taken, if you have not eaten (overnight).

We will take the first blood sample when you arrive at the hospital (in the morning) and then you will be asked to drink a sweet drink (glucose drink) and after two hours another blood sample will be taken. You will need to be at the hospital for at least two hours. After the blood is taken we send it to be tested to see you how your body is managing with the sugars you have been eating. We will give you some food to eat before you leave the clinic.

Labour and Delivery: You will stop taking the tablets, once your baby is delivered and information will be collected about how well you and your baby are.

28 days Postnatal Visit: After you have had your baby the study team will either ask you to visit the hospital or contact you to see how you and your baby are. During this visit, we will collect information about how you and your baby are this will be a short questionnaire.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART? We cannot be certain whether there are any benefits of taking metformin. However, the information we obtain, might help improve the future care for women who are overweight and pregnant in Malawi and at risk of developing diabetes. In the future, we hope to conduct a larger study to confirm this and your participation in PAPAGENO will help us develop further studies.

WHAT ARE THE POSSIBLE DISAVANTAGES OF TAKING PART? Some people may experience some side effects when taking the tablets for this study. The possible effects when taking metformin tablets are: nausea, vomiting, abdominal pain, diarrohea and reduced appetite. These are experienced in a small number of pregnant women (around 1 in 11). These effects are usually mild and are less likely when starting with a small dose of metformin and increasing slowly, as we will ask you to do. **A very rare complication of taking the tablets is a condition called lactic acidosis, where naturally occurring metabolic products build up in the blood stream. If one hundred thousand people take metformin for one year, one person is likely to have this condition: symptoms are extreme tiredness, cramps, diarrhea and vomiting**.

The placebo (dummy) tablet has no side effects and is safe. Note that although the use of metformin in pregnancy is recommended by some expert groups (including the UK National Institute of Health and Care Excellence) it is not advised by the manufacturer.

If you agree to participate in the main study and have side effects that concern you such as severe diarrohea and or vomiting, please stop your study medication immediately and contact the local study team. Your doctor or midwife may decide to change the number of tablets you take, as you might need a smaller dose.

Apart from having to take the tablets each day, there is the inconvenience of making extra hospital visits. We can try to arrange for these to be shared with your usual hospital visits to make it more convenient. **For one of the visits we will measure your body's response to sugar: we will ask you to fast from midnight the night before this visit.** Other than some

minor discomfort when taking blood, all the checks for this study are safe during pregnancy and have no harmful effects on you or your baby.

Taking part in the study will involve some of your time. We estimate that taking part will involve you in up to 10 hours of extra study visits, and around 5 mins per day at home over the 7 months of the study in taking the tablets and filling in the diaries.

You cannot take part in this study if you are taking Dolutegravir, please inform your study team, if you are taking this medication. You must also not drink alcohol whilst taking metformin. Drinking alcohol is not recommended for pregnant women. Your routine antenatal care will not change, if you do not participate in the study.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY? You can stop the study at any point. This will not affect your care but we would like to collect some information from your hospital records about your health and your baby's health. We will discuss this with you and we will ask you, if you are happy for us to carry on with data collection. The study team will use the data collected up until the date you withdraw and would like to collect information about your labour and delivery from your notes. If you do not want us to do this you must tell a member of the study team (or another member of the medical team) that you do not agree to this. We think it is important to collect this information, so that we can better understand the treatments.

PRIVACY AND CONFIDENTIALITY: We will keep the information you provide to us securely and with access restricted access. This information will be used only to contact you about the study by doctors or researchers running this trial. With your consent we will collect the following personal information about you: Your birth date, your address (GPS location) and local hospital identifier for both you and your baby.

We will collect your address (GPS location) so we can contact you at the end of the study with information about the results and with your permission, it may also be used to contact you again in the future, to see how you and your baby are doing. All the information we collect during the course of the research will be kept confidential and there are strict laws, which safeguard your privacy at every stage. However, with your permission, we would like to share anonymised information with other researchers**, regulatory bodies and commercial partners to monitor safety. The anonymized data will be used primarily for publications and monitoring safety.**

WHAT WILL WE DO WITH THE BLOOD SAMPLES? We will collect the blood from you and send this to a laboratory to be tested, at the end of the study. We will not tell you or your doctor the results until the study has finished. We will use this information to help us understand, if the treatments might help other women in the future. With your consent we would also like to keep a sample of your blood which will be stored in Malawi Epidemiology Intervention Research Unit (MEIRU Lilongwe). These blood samples will be used in this or future studies by the study team, for additional confirmatory testing of diabetes associated

conditions or conditions associated with poor maternal outcomes. These samples will be stored for 5 years. If you do not want your blood to be stored for this purpose you cannot participate in this study.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY? At the end of the study, we will be able to inform you of the study results if you wish. The results will be published in medical journals. You will not be identified in any report/publication. All information related to clinical studies in pregnancy is kept in secure storage in Edinburgh for at least 5 years. In Malawi it will be held for at least 3 years.

WHO DO I CONTACT IF I AM INJURED OR UNHAPPY WITH MY TREATMENT? You can contact the researchers who will inform the Sponsors of this study. This is the organisation who is responsible for ensuring it is conducted safely to report trial-related injuries or to appeal against a violation of your rights

WHO IS FUNDING THIS STUDY: Funding for PAPAGENO has been provided by the UK Department for International Development (DFID), the National Institute for Health Research (NIHR) the UK Medical Research Council (MRC), and the Wellcome Trust under the Joint Global Health Trials Initiative (**Project: MR/R019142/1).** The views and opinions are those of the authors and do not necessarily reflect those of the Funders.

DATA PROTECTION: The University of Edinburgh is the sponsor for this study. The Sponsor has overall responsibility for the running of the study. To follow the United Kingdom's data protection regulations we must inform you of how we will use and store your personal data.

As a university, we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

We will use information from you and/or your medical records in order to undertake this study. The sponsor will keep identifiable information about you for 5 years after the study has finished.

The University of Edinburgh will act as the data controller for this study. This means that they are responsible for looking after your information and using it properly.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already

obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

For more information please see the online privacy statement http://www.accord.scot/data-protection/our-privacy-notices

SPONSOR CONTACT:

Address: University of Edinburgh, the Queens Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ

Telephone: 0131 242 3330

Email: ACCORD research governance (resgov@accord.scot)

NAME AND CONTACT DETAILS OF THE PRINCIPAL INVESTIGATOR:

Address: Professor Mia Crampin

London School of Hygiene and Tropical Medicine,Malawi Epidemiology and Intervention Research Unit

Karonga Prevention Study
PO Box 148
Lilongwe Malawi

Telephone: +265999373980

Email: Mia.Crampin@lshtm.ac.uk

NHSRC CONTACTS:

Telephone: +265995903514

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STUDY APPROVAL

This study has been approved by

Address:

Telephone:

Email:

STUDY SITE

The study is taking place in Malawi at Indicate the site of the study Insert details

Address:

Telephone:

Email:

Thank you for taking the time to read this information sheet and for considering taking part.